NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A retrospective chart review of UK patients with relapsed/refractory acute lymphoblastic leukaemia treated with inotuzumab ozogamicin, a real world research study
Protocol number	X9001222
Protocol version identifier	V1.0
Date	18 July 2019
Active substance	Inotuzumab ozogamicin
Medicinal product	BESPONSA®
Research question and objectives	The purpose of this study is to describe the demographics and clinical characteristics, treatment pathway, and effectiveness and safety of inotuzumab ozogamicin in patients with relapsed/refractory B-cell acute lymphoblastic leukaemia treated with inotuzumab ozogamicin in the real-world. The objectives of the study are as follows: <u>Primary objective</u> • To describe the baseline demographic, clinical (including previous treatment) and laboratory characteristics of patients with relapsed/refractory B-cell acute lymphoblastic leukaemia at initiation of treatment with inotuzumab ozogamicin. <u>Secondary objectives</u> • To describe the inotuzumab ozogamicin treatment pathway, including inotuzumab ozogamicin doses, dose modifications and number of cycles of treatment; and concomitant medications. • To summarise complete remission or complete remission with incomplete

	haematological recovery rates following treatment with inotuzumab ozogamicin, overall and stratified according to the number of salvage therapies (0, 1, ≥2) received prior to inotuzumab ozogamicin initiation. • To summarise minimal residual disease negativity rates following initiation of inotuzumab ozogamicin, and describe the number of cycles of inotuzumab ozogamicin needed to attain minimal residual disease negativity. • To describe overall survival, and cause of death; in all patients and in patient with or without follow-up hematopoietic stem-cell transplantation. • To describe relapse-free-survival; in all patients and in patient with or without follow-up hematopoietic stem-cell transplantation. Additionally, to describe non-relapse mortality in patients undergoing follow-up hematopoietic stem-cell transplantation. • To describe the treatments for acute lymphoblastic leukaemia and responses to treatment post-inotuzumab ozogamicin, including hematopoietic stem cell transplantation, chemotherapy regimens and chimeric antigen receptor T-cell therapy. • To describe the occurrence of safety events including veno-occlusive disease /sinosuidal obstruction syndrome, grade 3/4 treatment-related adverse events (lung/cardiac/kidney) and other liver dysfunction following inotuzumab ozogamicin initiation; in all patients and in patients with or without follow-up hematopoietic stem-cell transplantation. In addition, to evaluate associations between risk factors identified in the INO-VATE acute lymphoblastic leukaemia trial and risk for veno-occlusive disease /sinosuidal

	obstruction syndrome in patients with follow-up hematopoietic stem cell transplantation.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ALL	Acute Lymphoblastic Leukaemia
CR	Complete Remission
InO	Inotuzumab Ozogamicin
MRD	Minimal Residual Disease
VOD	Veno-occlusive Disease
SOS	Sinusoidal Obstruction Syndrome
TRAE	Treatment Related Adverse Event
HSCT	Hematopoietic Stem Cell Transplant
EMA	European Medical Agency
UK	United Kingdom
NICE	National Institute for Health and Care Excellence
CUP	Compassionate Use Program
NHS	National Health Service
EU	European Union
CRi	Complete Remission with incomplete hematological recovery
OS	Overall Survival
RFS	Relapse-free Survival
NRM	Non-relapse Mortality
CAR	Chimeric Antigen Receptor
ECOG	Eastern Cooperative Oncology Group
ANC	Absolute Neutrophil Counts
ALT	Alanine Transaminase (also known as alanine aminotransferase)
AST	Aspartate Transaminase (also known as aspartate aminotransferase)
ALP	Alkaline Phosphatase
GGT	Gamma-Glutamyl Transferase
CCI	CCI
eCRF	Electronic Case Report Form
MLL	Mixed Lineage Leukaemia
ULN	Upper Limit of Normal
CI	Confidence Interval
SDV	Source Data Verification
IRB	Institutional Review Board
IEC	Independent Ethics Committee
GPP	Good Pharmacoepidemiology Practices
ISPE	International Society for Pharmacoepidemiology
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

GDPR	European Union General Data Protection Regulation
AE	Adverse Event
NI	Non Interventional
AEM	Adverse Event Monitoring
SRSD	Single Reference Safety Document
STROBE	Strengthening The Reporting of Observational studies in Epidemiology
ICMJE	International Committee of Medical Journal Editors

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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PPD, PhD			
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4. ABSTRACT

A retrospective chart review of United Kingdom (UK) patients with relapsed/refractory acute lymphoblastic leukaemia treated with inotuzumab ozogamicin, a real world research study.

Inotuzumab ozogamicin (InO) is a CD22 monoclonal antibody that was shown to improve outcomes of patients with relapsed/refractory B-cell acute lymphoblastic leukaemia (ALL) or Philadelphia chromosome positive ALL. In the phase III INO-VATE ALL study, patients receiving InO versus standard chemotherapy achieved significantly higher complete remission (CR) rates and minimal residual disease (MRD)-negativity rates. Veno-occlusive disease (VOD) / sinusoidal obstruction syndrome (SOS) was reported in INO-VATE ALL as a treatment related adverse event (TRAE), on average two weeks after end of treatment with InO, and especially in patients who had follow-up hematopoietic stem cell transplant (HSCT) therapy.

InO was approved by the European Medicines Agency (EMA) in June 2017. InO recently gained recommendation from the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) in line with the licensed indication on 9th August 2018, and is now available in routine care practice throughout the UK. Prior to NICE approval, InO was made available to UK patients through a compassionate use program (CUP) run by Pfizer Inc. between June 2016 and October 2017, and via private purchase. As part of the CUP alone, approximately 75 patients were treated across 31 National Health Service (NHS) Trusts, each Trust treating between 1 and 15 patients. Patient level data is available in medical records, enabling a retrospective chart review to be conducted.

There is a paucity of information on clinical outcomes in UK patients with relapsed/refractory B-cell ALL treated with InO outside of the context of clinical trials. The number of patients enrolled in INO-VATE ALL from the UK was limited. In this context, a retrospective chart review evaluating real world effectiveness and safety of InO for ALL when administered in routine care in the UK is of interest to clinicians and patients.

The purpose of this study is to describe the demographics and clinical characteristics, treatment pathway, and effectiveness and safety of InO in patients with relapsed/refractory B-cell ALL treated with InO in the UK.

The objectives of the study are as follows:

Primary objective:

- To describe the baseline demographic, clinical (including previous treatment) and laboratory characteristics of patients with relapsed/refractory B-cell ALL at initiation of treatment with InO.

Secondary objectives:

- To describe the InO treatment pathway, including InO doses, dose modifications and number of cycles of treatment; and concomitant medications.
- To summarise CR or CR with incomplete haematological recovery (CR/CRi) rates following initiation of InO, overall and stratified according to the number of salvage therapies (0, 1, ≥2) received prior to InO initiation.
- To summarise MRD negativity rates following initiation of InO, and describe the number of cycles of InO needed to attain MRD negativity.
- To describe overall survival (OS) and cause of death; in all patients and in patient with or without follow-up HSCTTo describe relapse-free-survival (RFS) in all patients and in patients with or without follow-up HSCT. Additionally, to describe non-relapse mortality (NRM) in patients undergoing follow-up HSCT.
- To describe the treatments for ALL and responses to treatment post InO, including HSCT, chemotherapy regimens and chimeric antigen receptor (CAR) T-cell therapy
- To describe the occurrence of safety events including documented diagnoses of VOD/SOS, grade 3/4 TRAEs (lung/cardiac/kidney) and other liver dysfunction following InO initiation; in all patients and in patients with or without follow-up HSCTIn addition, to evaluate associations between risk factors identified in the INO-VATE ALL trial and risk for VOD/SOS in patients with follow-up HSCT.

This is a UK, multi-centre, retrospective, non-interventional cohort study based on secondary use of hospital medical records (paper-based and/or electronic, as appropriate).

Key definitions

- The index date: the date of initiation of the first cycle of InO.
- The baseline period: period from 6 months prior to index date to index date. The closest observation recorded during the baseline period and closest to index date will be used as baseline data (when more than one observations are available).
- Pre-index observation period: period from the date of ALL diagnosis to the index date.
- Post-index observation period: period from the index date until the date of death, or date of latest visit at the time of data collection, whichever is soonest.
- CR/CRi rate: number of patients who achieve CR/CRi divided by the total number of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO).

- MRD negativity rate: proportion of patients in whom MRD-negative status is observed, among patients in whom MRD negativity status has been assessed, at any time until the end of treatment with InO (defined as the date of recorded discontinuation of InO).
- OS: time from index date to death.
- RFS: time from index date to the earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), and start of new induction therapy or post-therapy HSCT without achieving CR/CRi.
- NRM: Time from the date of follow-up HSCT until death without disease progression or relapse. Deaths from any cause without prior progression are events. Events related to the disease such as relapse, progression are competing events, loss to follow-up are censored

Patients will be observed from the start of the pre-index observation period until the end of the post-index observation period. Patients who have not completed 1 year of follow-up after index date and are still alive will be censored at the latest visit date at the time of data collection.

The source population for this study is adult patients treated with InO at the selected sites and who accessed InO *via* NHS commissioning, *via* the CUP or *via* private purchase between June 2016 and date of data collection (to be confirmed). The NICE recommendation is as an option for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia in adults; and patients with relapsed or refractory Philadelphia chromosome positive disease should have had at least 1 tyrosine kinase inhibitor. The eligibility criteria for inclusion into the CUP is provided in Section 14 Annex 1.

Patients will be eligible for inclusion in the present study if they fulfill all of the following criteria:

Inclusion criteria

- Patients with relapsed/refractory ALL.
- Patients who initiated InO between 1st of June 2016 and date of data collection (to be confirmed).
- Patients who accessed InO treatment *via* NHS commissioning, *via* the CUP, or *via* private purchase.
- Patients aged ⩾18 years old at initiation of InO treatment

Exclusion criteria

- Patients initiated on treatment with InO at a different hospital than the ones selected in this study.

- Patients with <3 months of follow-up since index date, unless death occurs <3 months from index date.

Consent will not be required as all identifiable patient data (from surviving and deceased patients) will be extracted by the patient's direct medical care team. Eligible patients will be selected by chronological order and with a priority given to patients treated *via* NHS commissioning, where possible.

Dataset

The following data will be collected from patients medical records in order to address the objectives of the study:

- Patient demographics and clinical and laboratory characteristics (including details of age, sex, Eastern Cooperative Oncology Group (ECOG), ALL diagnosis, type and stage, liver disease history, ALL-related treatment history, hematological and biochemical laboratory evaluations)

- InO treatment pathway (including details of InO doses, dose modifications, treatment duration, number of cycles and duration of each cycle, reason for interruption of cycle)

- Azole antifungal therapy concomitant to InO treatment

- InO treatment outcomes (including details of treatment response assessments, disease progression, death)

- Treatments post-InO (including new chemotherapy regimen, HSCT, CAR-T) and responses to treatment (CR, CRi, stable disease, progressive disease)

- Safety events (including details of documented diagnoses of VOD/SOS, grade 3/4 TRAEs and other liver dysfunction and risk factors for VOD/SOS) and treatment for those events.

Data will be collected retrospectively from patients' hospital medical records (paper-based and electronic) by members of the direct care team. Data will be collected using a pseudonymised electronic case report form designed specifically for the study. Participants will be identified in all study records by a unique participant identification number to allow data management queries to be resolved with reference to source medical records while preserving patient confidentiality.

Three to five of the 31 NHS Trusts participating in the CUP that individually treated the largest number of patients with InO as part of the CUP (total number of patients including private purchase to be confirmed), will initially be selected for this study to achieve a target sample size of approximately 25 patients (the number of sites may be expanded at a later date).

Analyses will be performed by pH Associates using Stata (StataCorp LLC) and R statistical software. Data from the selected sites will be pooled for analysis. Data will be analysed according to a pre-defined statistical analysis plan that will be finalised before data collection is completed.

Descriptive statistics (numbers, percentages, means, standard deviations, medians, quartiles, minimum, maximum, number of missing and non-missing values), as appropriate to the data collected, will be used to describe baseline demographic and clinical characteristics, treatment pathway, outcomes and TRAEs for the overall study population. Ninety-five percent confidence intervals (95% CI) for CR/CRi rates and MRD negativity rates will be estimated using an exact Poisson regression. Patients who are still alive and have not progressed at the last visit date without clinical evidence of progression will be censored. Median time to CR/CRi, and median OS and RFS, and corresponding 95% CI, will be estimated using the Kaplan-Meier method.

CCI

A data analysis plan that further details the output, including table shell, to be included in the study report will be provided in a separate document, prior to data analysis.

Data collection will commence from the date relevant approvals from each of the participating centres are in place to conduct the study, and is anticipated to last for approximately four months

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned date
Start of data collection	01 September 2019
End of data collection	15 January 2020
Final study report	01 March 2020

7. RATIONALE AND BACKGROUND

Acute lymphoblastic leukaemia (ALL) is an acute form of leukemia which affects the white blood cells (B cells or T cells), that is aggressive and progresses rapidly, requiring immediate treatment. The incidence of ALL in the UK is 1.5 per 100,000 in males and 2 per 100,000 in females[1].

ALL is a disease characterised by malignant transformation and proliferation of lymphoid progenitor cells in the bone marrow, blood and extramedullary sites[2]. Patients with relapsed or refractory acute ALL have less than 50% chance of achieving a complete remission (CR), with a median relapse-free survival (RFS) of only 5.2 months[3]. The 5-year overall survival rate has been estimated as 7% overall, and is higher in younger patients: 12% in patients aged under 20 years *versus* 3% in patients over 50 years[4].

Several novel therapies have been recently approved for relapsed/refractory B-cell ALL with the aim to maintain remission and prolong survival[5]. Antibody-drug conjugates (ADC) are a class of novel emerging therapies that target the cell surface or intracellular antigens specific for leukaemic cells, thus sparing cell death in the normal and off target tissues[5]. Inotuzumab ozogamicin (InO) is a CD22 monoclonal antibody that was shown to improve outcomes of patients with relapsed/refractory B-cell ALL or Philadelphia chromosome positive ALL.

In the phase III INO-VATE ALL study, patients receiving InO versus standard chemotherapy achieved significantly higher response (CR rate was 80.7% [95% confidence interval [CI], 72%–88%] vs 29.4% [95% CI, 21%–39%]) and minimal residual disease (MRD)-negativity rates (78.4% [95% CI, 68%–87%] vs 28.1% [95% CI, 14%–47%])[6]. Progression-free survival (median was 5.0 [95% CI, 3.7–5.6] vs 1.8 [95% CI, 1.5–2.2] months) and overall survival (median was 7.7 (95% CI, 6.0–9.2) vs 6.7 (95% CI, 4.9–8.3) months) were also

prolonged in patients treated with InO versus standard chemotherapy[6].

Veno-occlusive disease (VOD; also known as sinusoidal obstruction syndrome [SOS]) was reported in INO-VATE ALL as a treatment related adverse event (TRAE) occurring on average 16 days after the last dose of InO, and especially in patients who proceeded onto hematopoietic stem cell transplant (HSCT) therapy after InO treatment [6,7]. Occurrence of VOD/SOS was 13% in patients receiving InO versus <1% in patients receiving standard of care, and 22% versus 3%, respectively, in patients with follow-up HSCT[7]. Additional characteristics at initiation of treatment with InO and at follow-up HSCT were also tested by Kantarjian et al. that may help identify patients with follow-up HSCT most at risk of developing VOD/SOS[7]. Non-haematologic TRAEs were also observed which affected the lung, cardiac system and kidney[6,8].

InO was approved by the European Medicines Agency (EMA) in June 2017 for the treatment of adults with relapsed/refractory CD22-positive B-cell ALL and for adults with Philadelphia chromosome positive relapsed/refractory B-cell ALL who have failed previous treatment, to be marketed as BESPONSA®. BESPONSA® is administered in 3- to 4- week cycles at doses of 1.5 mg/m^2 to 1.8 mg/m^2 for a total duration of 2-3 cycles in patients proceeding to HSCT (third cycle added for patients not achieving CR/CRi and MRD negativity), and up to 6 cycles otherwise [6].

InO recently gained recommendation from the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) in line with the licensed indication on 9th August 2018[9] (see **Annex 1**), and is now available in routine care practice throughout the UK. Prior to NICE approval, InO was made available to UK patients through a compassionate use program (CUP) run by Pfizer Inc. between June 2016 and October 2017 (see **Annex 1**), and *via* private purchase. As part of the CUP alone, approximately 75 patients were treated across 31 National Health Service (NHS) Trusts, each Trust treating between 1 and 15 patients. Patient level data is available in medical records, enabling a retrospective chart review to be conducted.

There is a paucity of information on the descriptive characteristics, treatment patterns and clinical outcomes in patients with relapse/refractory B-ALL treated with InO outside of the context of clinical trials[9]. The number of patients enrolled in INO-VATE ALL was also relatively limited [6]. In this context, and considering that InO is the only ADC currently available to ALL patients in the European Union (EU), a retrospective chart review evaluating real world effectiveness and safety of InO for ALL when administered to adult patients in routine care in the UK is of interest to clinicians and patients.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to describe the demographics and clinical characteristics, treatment pathway, and effectiveness and safety of InO in patients with relapsed/refractory B-cell ALL treated with InO in the real-world.

The objectives of the study are as follows.

Primary objective:

- To describe the baseline demographic, clinical (including previous treatment) and laboratory characteristics of patients with relapsed/refractory B-cell ALL at initiation of treatment with InO.

Secondary objectives:

- To describe the InO treatment pathway, including InO doses, dose modifications and number of cycles of treatment; and concomitant medications.
- To summarise CR or CR with incomplete haematological recovery (CR/CRi) rates at completion of treatment with InO, overall and stratified according to the number of salvage therapies (0, 1, ≥2) received prior to InO initiation.
- To summarise MRD negativity rates in patients assessed for MRD negativity, at completion of treatment with InO, and describe the number of cycles of InO needed to attain MRD negativity.
- To describe overall survival (OS), and cause of death; in all patients and in patient with or without follow-up HSCT.
- To describe RFS; in all patients and in patient with or without follow-up HSCT. Additionally, to describe non-relapse mortality (NRM) in patients undergoing follow-up HSCT.
- To describe the treatments for ALL and responses to treatment post InO, including HSCT, chemotherapy regimens and chimeric antigen receptor T-cell therapy
- To describe the occurrence of safety events including documented diagnoses of VOD/SOS, grade 3/4 TRAEs (lung/cardiac/kidney) and other liver dysfunction following InO initiation; in all patients and in patients with or without follow-up HSCT. In addition, to evaluate associations between risk factors identified in the INO-VATE ALL trial and risk for VOD/SOS in patients with follow-up HSCT.

9. RESEARCH METHODS

9.1. Study design

This is a UK, multi-centre, retrospective, non-interventional cohort study based on secondary use of hospital medical records (paper-based and/or electronic, as appropriate). Three to five out of the 31 NHS Trusts that treated the largest number of patients with InO as part of the CUP will be initially selected for this study (the number of centres may be further expanded). A retrospective design has been selected as data have already been recorded into medical records and are available for data collection. The study is non-interventional as all patients received InO as part of routine clinical care, either *via* enrolment into the CUP or *via* private purchase.

Endpoints related to the primary objective are as follows and will be further described in Section 7.3:

- Summary measures of demographic characteristics (age and sex)
- Summary measures of clinical characteristics, including date of disease, stage of disease , C22-positive/negative, ALL cytogenetics, and Eastern Cooperative Oncology Group (ECOG) performance status, number of relapses prior to InO initiation.
- Summary measures of ALL-related treatments prior to InO initiation, and response to treatment.
- Baseline laboratory measurement including: blood indicators (full blood counts, platelets and absolute neutrophil counts [ANC]), liver function tests alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, albumin and gamma glutamyl transferase (GGT).

Endpoints related to the secondary objective are as follows and will be further described in Section 7.3:

- Summary measures of InO treatment including: duration, number of cycles per patient, dose at initiation, dose modifications and discontinuation status (including reasons).
- Summary measures of azole antifungal therapy concomitant to InO treatment.
- Summary measures of CR, CRi and CR/CRi rates at end of InO cycles of treatment; overall and according to the number of salvage therapies in the pre-index observation period (0, 1, ≥2).
- Summary measures of MRD negativity at the end of InO cycles of treatment; and the number and proportion of patients attaining MRD negativity overall and according to the number of completed cycles of InO at the time of attainment (after 1, 2, ≥3 cycles of InO).
- The number and proportion of patients surviving at 3, 6 and 12 months after InO initiation, and cause of death; overall and in patients with and without HSCT.

- Median OS (95% CI); overall and in patients with and without HSCT.
- The number and proportion of patients who are relapse-free at 3, 6 and 12 months after InO initiation; overall and in patients with and without HSCT.
- Median RFS (95% CI); overall and in patients with and without HSCT.
- Median NRM (95% CI) in patients undergoing follow-up HSCT from the date of HSCT.
- Number and proportion of patients undergoing follow-up HSCT, initiating chimeric antigen receptor (CAR) -T cell therapy, and initiating chemotherapy regimens after InO treatment.
- Number and proportion of patients experiencing documented diagnoses of VOD/SOS during the post-index observation period, overall, by grade and in the subset of patients (1) post-chemotherapy and (2) post-HSCT; treatment received for VOD/SOS including defibrotide and heparin.
- Number and proportion of patients experiencing grade 3/4 TRAEs (lung / cardiac / kidney) following InO initiation. Name of grade 3/4 TRAEs (lung / cardiac / kidney), name of treatment received, dose reduction / discontinuation of InO following TRAEs
- Number and proportion of patients experiencing other liver dysfunction following InO initiation. Name of liver dysfunction, name of treatment received, dose reduction / discontinuation of InO following TRAEs.
- CCI [redacted]

9.2. Setting

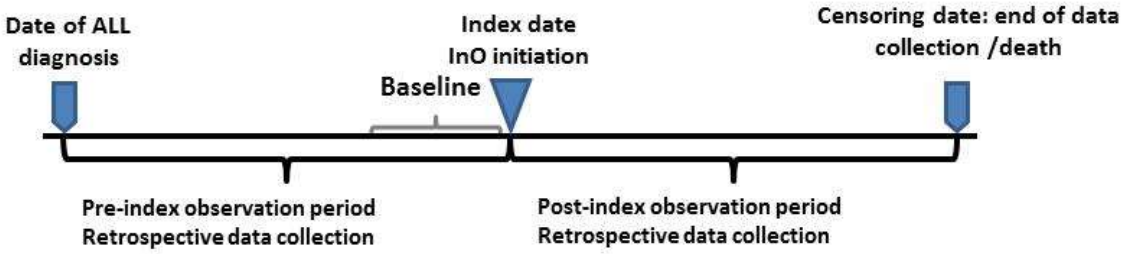
Key definitions

- Index date: the date of initiation of the first cycle of InO.
- Baseline period: period from 6 months prior to index date to index date. The closest observation recorded during the baseline period and closest to index date will be used as baseline data (when more than one observations are available).
- Pre-index observation period: period from the date of ALL diagnosis to the index date.
- Post-index observation period: period from the index date until the date of death, or date of latest visit at the time of data collection, whichever is soonest.
- CR/CRi rate: number of patients who achieve CR/CRi divided by the total number of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO).

- MRD negativity rate: proportion of patients in whom MRD-negative status is observed, among patients in whom MRD negativity status has been assessed, at any time until the end of treatment with InO (defined as the date of recorded discontinuation of InO).
- OS: time from index date to death.
- RFS: time from index date to the earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), and start of new induction therapy or post-therapy HSCT without achieving CR/CRi.
- NRM: Time from the date of follow-up HSCT until death without disease progression

Patients will be observed from the start of the pre-index observation period until the end of the post-index observation period. For the purpose of identifying risk factors for VOD/SOS and replicating the findings by Kantarjian et al.[7], follow-up will be defined as the post-index observation period, and patients will be censored at the date of the last recorded clinic visit prior to data collection.

Figure 1: Study design and observation periods



Three to five of the 31 NHS Trusts participating in the CUP that treated the largest number of patients with InO as part of the CUP (total number of patients including private purchase to be confirmed) will initially be selected for this study to achieve a target sample size of approximately 25 patients (the number of sites may be expanded at a later date). The list of selected sites will be maintained in a stand-alone document. Sites will be selected on the basis that:

- Their cancer service participated in the CUP.
- They treated at least 1 adult patient with InO *via* the CUP.
- They have an interest in taking part in the study.

- They have appropriate and sufficient personnel available locally to identify eligible patients, collect the required data from medical records and to appropriately conduct the study in accordance with applicable legal and regulatory requirements.

9.2.1. Inclusion criteria

The source population for this study is adult patients treated with InO at the selected sites and who accessed InO *via* NHS commissioning, *via* the CUP or *via* private purchase between June 2016 and February 2019 The NICE recommendation is as an option for treating relapsed or refractory CD22- positive B-cell precursor ALL in adults; and patients with relapsed or refractory Philadelphia chromosome positive disease should have had at least 1 tyrosine kinase inhibitor[9] (see **Annex 1** for NICE eligibility criteria). The eligibility criteria for inclusion in the CUP are provided in Annex 1.

Patients will be eligible for inclusion in the present study if they fulfill all of the following criteria:

Inclusion criteria

- Patients with relapsed/refractory ALL.
- Patients who initiated InO between 1st of June 2016 and date of data collection.
- Patients who accessed InO treatment *via* NHS commissioning, via the CUP, or via private purchase.
- Patient aged ⩾18 years old at initiation of InO treatment

Exclusion criteria

- Patients initiated on treatment with InO at a different hospital than the ones selected in this study.
- Patients with <3 months of follow-up since index date, unless death occurs <3 months from index date.

Eligible patients will be selected by chronological order and with a priority given to patients treated *via* NHS commissioning, if possible.

9.3. Variables

The endpoints associated with each of the study objectives are described below, along with the variables that will be collected in order to address the objectives. Response options for each variable will be further detailed in the electronic case report form (eCRF). A list of data items to be collected and operational definitions for clinical endpoints are provided in Annex 2.

Table 1: List of endpoints and variables required to address the objectives of the study

Endpoint to address the primary objective	Dataset required to address the primary objective
Primary objective: To describe the baseline demographic, clinical (including previous treatment) and laboratory characteristics of patients with relapsed/refractory B-cell ALL at initiation of treatment with InO.	

Summary measures of:
• Demographic characteristics:
  o Age at index date
  o Sex
• Clinical characteristics:
  o ECOG performance status at baseline.
  o Date of ALL diagnosis.
  o Phase of disease at index date: CR, 1st relapse, 2nd relapse , 3rd relapse, 4th or greater relapse
  o CD22 expression: percentage of positive cell blasts
  o ALL cytogenetics; mixed lineage leukaemia (MLL)-AF4; BCR-ABL; low hypodiploidy/near triploidy; complex karyotype
  o Number of ALL relapses prior to index date
  o History of liver diseases prior to index date (before or after diagnosis), and whether they were ongoing or resolved at index date.
• Laboratory characteristics at baseline
  o Full blood counts, including: platelets and ANC
  o Liver function tests including: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, albumin, gamma glutamyl transferase (GGT).
	Dates are DD/MM/YYYY unless specified
	• Date of InO initiation
	• Date of birth (MM/YY)
	• M/F
	• Date of initial diagnosis of ALL.
	Recorded during baseline period and closest prior to index date:
	• ECOG performance status results
	• Phase of disease at index date: CR, 1st relapse, 2nd relapse , 3rd relapse, 4th or greater relapse
	• Pre-existing liver disease ongoing/resolved (Y/N).
	• Percentage of positive cell blasts (CD22 expression test)
	• Result for test for ALL cytogenetics: MLL-AF4; BCR-ABL; low hypodiploidy/near triploidy; complex karyotype
	• ALL relapses prior to index date: dates
	• Results and date of liver function tests results including: ALT, AST, ALP, bilirubin, albumin, GGT.
	• Results and date of full blood counts results including: platelets and ANC
	
	Anytime between initial diagnosis of ALL and InO initiation:
	• 1st line chemotherapy according to national trial or treatment guideline
	• Number of lines of salvage therapy
	• Number of prior HSCT, conditioning regimen for each HSCT (high-dose myeloablative, reduced-intensity, nonmyeloablative)
	• Treatment with blinatumomab: yes/no
	• Number of CAR T-cell treatments

• ALL-related treatment prior to InO initiation: o 1st line chemotherapy according to national trial or treatment guideline o Summary of number of patients by; ▪ number of lines of salvage therapy: 0, 1, 2, ⩾3 ▪ number of prior HSCT (0, 1, 2, ⩾3) and by type of conditioning regimen for each HSCT (high-dose myeloablative, reduced-intensity, nonmyeloablative [10]) ▪ Treated with blinatumomab ▪ Number of CAR T-cell therapies: 0, 1, ⩾2	
Endpoints to address the secondary objectives	**Dataset required to address the secondary objectives**
Secondary objective: To describe the InO treatment pathway, including InO doses, dose modifications and number of cycles of treatment; and concomitant medications.	
Summary measures of: • Total duration of treatment with InO • Number of cycles of InO per patient • Interrupted cycles of InO, including reasons (liver toxicity TRAEs, other AEs, tolerance, treatment failure, and course complete). • Doses of InO prescribed • Modification of doses of InO, including reasons (liver toxicity TRAEs, other AEs, tolerance, treatment failure, and course complete). • Azole antifungal therapy concomitant to InO treatment	Dates are DD/MM/YYYY unless specified • InO treatment: start date and end date of each cycle, cycle completed / interrupted (if interrupted provide reason for discontinuation) • Azole antifungal therapy including fluconazole, voriconazole, itraconazole and posaconazole (and other indicated in the medical records): date started, date end.
Secondary objective: To summarise CR/CRi rates following initiation of InO, overall and according to the number of salvage therapies received prior to InO initiation.	

Summary measures of: • CR, CRi and CR/CRi response rates by the end of InO treatment, overall and according to the number of salvage therapies in the pre-index observation period (0, 1, ⩾2). • Median time to CR/CRi (95% CI)	Dates are DD/MM/YYYY unless specified • Date of start and stop of InO treatment (stop date is date of discontinuation) • Response to InO treatment first recorded after end of treatment: date, response (CR, CRi, stage disease, progression) • Number of salvage therapies for ALL prior to index date.
Secondary objective: To summarise MRD negativity rates following initiation of InO, and describe the number of cycles of InO needed to attain MRD negativity.	
• Number and proportion of patients achieving MRD negativity overall and by the number of completed cycles of InO (after 1, 2, ⩾3 cycles of InO) in patients evaluated by flow-cytometry/ molecular assessment / both.	Dates are DD/MM/YYYY unless specified • Date of InO initiation • Start and stop date of each cycle of InO • Date of discontinuation of InO • MRD negativity recorded: Y/N. If Y test performed (flow cytometry, molecular assessment, both), result: negative / positive, date of test.
Secondary objective: To describe OS, and cause of death; in all patients and in patient with or without follow-up HSCT.	
Summary measures of, in all patients, and separately in patients with and without follow-up HSCT: • The number and proportion of patients surviving at 3, 6 and 12 months after InO initiation • Cause of death • Median OS (95% CI)	Dates are DD/MM/YYYY unless specified • Date of InO initiation • Patient with follow-up HSCT: Yes/No • Patient alive at data collection (Y/N) • For deceased patients: date and cause of death leukaemia or TRM • For surviving patients: date of last visit before data collection
Secondary objective: To describe RFS in all patients and in patients with or without follow-up HSCT. Additionally, to describe NRM in patients undergoing follow-up HSCT.	
Summary measures of, in all patients, and separately in patients with and without follow-up HSCT: • The number and proportion of patients who are relapse-free at 3, 6 and 12 months after InO initiation • Median RFS (95% CI) In patients undergoing follow-up HSCT:	Dates are DD/MM/YYYY unless specified • Date of InO initiation • Patient with follow-up HSCT: Yes/No • Patient alive at data collection (Y/N) • For deceased patients: date and cause of death • For surviving patients: date of last visit before data collection.

• Median NRM (95% CI) from the date of follow-up HSCT	• Dates of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), and start of new induction therapy or post-therapy HSCT without achieving CR/CRi; as documented in medical records (if unavailable, infer using definitions above).
Secondary objective: To describe the treatments for ALL and responses to treatment post-InO, including HSCT, chemotherapy regimens and CAR T-cell therapy	
For each treatment post-InO including: new chemotherapy (blinatumomab, other), HSCT, CAR T cell therapy, report: • number and proportion of patients initiated on treatment (for HSCT report number of HSCT) • response to treatment: CR, CRi, progressive disease, stable disease • Survival: number of patients alive / dead at completion of treatment	Dates are DD/MM/YYYY unless specified • Stop date of InO treatment • List of treatments started post-InO: new chemotherapy (blinatumomab, other), HSCT (record if several HSCT), CAR-T cell therapy • Response to treatments post InO: CR, CRi, progressive disease, stable disease • Survival: whether alive / dead at completion of treatment
Secondary objective: To describe the occurrence of safety events including documented diagnosis of VOD/SOS, grade 3/4 TRAEs (lung/cardiac/kidney) and other liver dysfunction following InO initiation; in all patients and in patients with or without follow-up HSCT. In addition, to evaluate associations between risk factors identified in the INO-VATE ALL trial and risk for VOD/SOS in patients with follow-up HSCT.	
Summary measures of, in all patients, and separately in patients with and without follow-up HSCT: • Number and proportion of patients experiencing a documented diagnosis of VOD/SOS during the post-index observation period, overall, by grade, and in the subsets of patients (1) with follow-up chemotherapy after completion of chemotherapy, and (2) with follow-up HSCT after HSCT • Treatments received for documented diagnoses of VOD/SOS including defibrotide and heparin and survival following treatment (patient alive / dead, cause of death)	Dates are DD/MM/YYYY unless specified • Date of InO initiation • Date of InO discontinuation and reason • Date of birth (MM/YY) • Documented diagnosis of VOD/SOS diagnosis: Y/N, if Y: start and end dates, grade, treatment for VOD/SOS including defibrotide and ursodeoxycolic acid • Treatment for documented diagnosis of VOD/SOS: list (defibrotide, ursodeoxycolic acid, other[specify]), patient alive / dead at end of treatment (cause of death) • Grade 3/4 TRAEs (lung/cardiac/kidney) diagnoses: start and end dates, grade • Dates and results for liver function tests including ALT, AST and bilirubin immediately

• Number and proportion of patients with InO dose delay/reduction/discontinuation due to VOD/SOS • Number and proportion of patients experiencing grade 3/4 TRAEs (lung / cardiac / kidney) following InO initiation, by type • Treatments received and InO dose delay/reduction/discontinuation for grade 3/4 TRAEs (lung/cardiac/kidney) • Number and proportion of patients experiencing other liver dysfunction following InO initiation, by type • Treatments received and InO dose delay/reduction/discontinuation for other liver dysfunction • Peripheral blood blast counts of patients prior to follow-up HSCT • Number and proportion of patients with significant risk factors for VOD/SOS measured at the time of follow-up HSCT (see below, extracted from Table 5 in Kantarjian et al.[2]), separately in patients developing and not developing VOD/SOS. CCI [redacted]	prior to follow-up HSCT (HSCT recorded during the post-index observation period): • Date and results for peripheral blood blast counts closest prior to follow-up HSCT • Conditioning regimens prior to HSCT including Busulfan, other alkylating agents: names and date start, date end, full intensity / reduced intensity conditioning • Date of HSCT • Date of completion of chemotherapy treatment

Kantarjian et al [7] identified risk factors for the occurrence of a documented diagnosis of VOD/SOS in patients who proceeded to follow-up HSCT after initiation of InO. The list of significant patient characteristics and transplant characteristics at the time of follow-up HSCT (with p-value<0.05) was as follows:

- Identified using univariate logistic regression:
    - Conditioning regimen with two alkylating agents (two versus one) prior to follow-up HSCT
    - Busulfan-containing regimen (yes versus no) prior to follow-up HSCT
    - Last bilirubin concentration (≥Upper limit of normal [ULN] *vs* <ULN) measured prior to follow-up HSCT
    - Age (≥55 years *vs* <55 years)
- Identified using multivariate logistic regression:
    - Conditioning regimen with two alkylating agents (two *vs* one) prior to follow-up HSCT
    - Last bilirubin concentration (≥ULN *vs* <ULN) measured prior to follow-up HSCT. Last AST or ALT concentration (>1.5 × ULN *vs* ≤1.5 × ULN) measured prior to follow-up HSCT

9.4. Data sources

Data for this study will be initially collected through retrospective data collection from three to five NHS Trust cancer services in the UK which were part of the CUP (additional centres may be added at a later stage if the target sample size is not achieved).

Data on patient demographic and clinical characteristics, treatment patterns, outcomes, and AEs will be collected from paper based and/or electronic hospital medical records (as applicable at each site) by members of the patient's direct care team in anonymised-coded form.

Data will be collected using anonymized-coded eCRFs designed specifically for the study. Participants will be identified in all study records by a unique participant identification number to allow data management queries to be resolved with reference to source medical records while preserving patient confidentiality.

9.5. Study size

This is a descriptive study and there is no *a priori* hypothesis specified, therefore a formal power calculation is not required. The sample size of approximately 25 patients has been based on the number of patients expected to be available at three centres that individually treated the largest number of patients with InO.

For the assessment of risk factors for VOD/SOS in patients with follow-up HSCT, the following rationale applies regarding sample size. Usually, 10 events per variable are required to be able to fit a Cox proportional hazard model with sufficient accuracy[11]. The Kantarjian analysis identified 4 risk factors in a univariate analysis and 2 risk factors in the

multivariate analysis (See section 7.3). In addition, 47% of patients (77 out of 164 patients) had follow-up HSCT and VOD/SOS occurred in 22% of patients with follow-up HSCT in the INO-VATE ALL trial[7]. Therefore, it derives that for the univariate analysis (i.e., a model which fits one variable at a time), 45 patients with follow-up HSCT and 96 patients overall would be needed to be enrolled into the study. For the multivariate analysis fitted with the 2 significant risk factors previously identified, 90 patients with HSCT and 192 patients overall would be need to be enrolled. Therefore, considering the sample size of the study, if risk factors cannot be estimated using a multivariate model, all factors will be assessed using a univariate model, if possible.

9.6. Data management

Data management and handling of data will be conducted according to the study specific data management plan and in accordance with European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)/ International Society for Pharmacoepidemiology (ISPE)/ General Data Protection Regulation (GDPR) guidance. Data for the study will be collected via an electronic data capture system using a standardised eCRF designed specifically for the study in accordance with this protocol. All data will be collected from hospital medical records by members of the NHS direct care team.

Before the start of data collection, NHS staff collecting data from patients' hospital medical records will be trained in data entry into the eCRFs by study management staff from pH Associates and consistency checks will be built into the eCRF to ensure data quality.

Patients will be identified in all study records by a unique study code to link multiple study records for each participant (if applicable) and preserve patient confidentiality.

Data management for eCRFs will be carried out using MACRO™, a data management system which has a secure web-based data entry interface and is fully validated and compliant with Food and Drug Administration Information Governance standard 21 Code of Federal Regulations part 11. The MACRO™ system has restricted access permissions for data entry and data management, and records an audit trail of all changes to data and activity in the system in line with 21 Code of Federal Regulations part 11. Access to the study in MACRO™ will be restricted (by password protection) to only those members of staff directly involved with the study and assigned access permissions will control the level of access to that required for the role of each individual working on the study. If corrections are needed to an eCRF, queries will be raised in the electronic data capture system by the study data manager and these will be resolved by the responsible investigator (or designee) by reference to the source records.

After obtaining the appropriate local approvals for data release, the anonymised-coded study data will be collated and transferred securely to pH Associates, who will be the Data Processor for data management, analysis and reporting on behalf of Pfizer, the Data Controller.

7.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be *password protected or secured in a locked room* to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

7.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g. letters, meeting minutes, and

telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement, whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 5 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a separate statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

Analyses will be performed by pH Associates using Stata (StataCorp LLC) and R statistical software (version 3.4.1 or later). Data from all participating centres will be pooled for analysis.

Descriptive statistics (number, percentages, means, standard deviations, medians, quartiles, minimum, maximum, number of missing and non-missing values), as appropriate to the data collected, will be used to describe baseline demographic and clinical characteristics for the overall study. Treatment patterns, treatment outcomes and TRAEs will also be reported using descriptive characteristics. Frequency and percentages will be used to describe categorical variables. All percentages will be reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding. Means, standard deviations, medians, quartiles, minimum, and maximum, will be used to describe continuous variables. Patients who are still alive and have not progressed at the last visit date without clinical evidence of progression will be censored. Kaplan-Meier plots will be used to describe data related to OS, RFS and time to CR/CRi. A summary table of the number of events and censored patients at each monthly interval will also be included.

The CR/CRi rate will be estimated as the proportion of patients who achieve CR/CRi divided by the total number of patients completing treatment with InO (defined as patients with a recorded date of discontinuation of InO). The MRD negativity rate will be defined as the proportion of patients in whom MRD-negative status is observed, among patients in whom MRD negativity status has been assessed, at any time until the end of treatment with InO (defined as the date of recorded discontinuation of InO). Patients who have not completed treatment with InO will not be included in CR/CRi rate and MRD negativity rate estimations. Date of 95% confidence intervals (CI) for CR/CRi rates and MRD negativity rates will be estimated using the Clopper-Pearson method. OR, RFS and NRM will be implemented according to their definition.

CCI [redacted]

Where dates are ambiguous because of missing day and/or months, standard imputation will be applied: where day is missing the 15th of the month will be assumed; where both day and month are missing the 1st July will be assumed. Where data other than dates are missing from the original medical record, the affected analyses will be conducted using only the results of those patients with data available and the number included in each analysis will be stated. The percentage of data missing will be reported for each study variable. Note that the multivariate model will only include those patients with non-missing values for all covariates.

9.8. Quality control

All data collectors will be provided with Data Collection Guidelines to facilitate consistent completion of the eCRF and will receive training in the requirements of the study protocol and correct completion of the eCRF prior to commencement of data collection.
The accuracy and quality of data collection will be monitored by reference to source data (source data verification [SDV]).

SDV will be performed on the complete dataset of a random sample of at least 10% of patients from each centre. Any issues identified by pH Associates relating to quality, accuracy or consistency of data collection will be discussed with the data collector concerned

and further training provided by pH Associates if required. If any subsequent issues are identified related to quality, accuracy or consistency of data collection, a random check of a further 10% of data collected by that data collector will be undertaken. Should any further issues be identified, 100% SDV will be undertaken at the centre. It is the Investigator's responsibility at each centre to ensure the accuracy of the data entered into the CRFs.

A 'back-to-back' SDV monitoring methodology will be performed with a member of the direct care team. This will involve the direct care team member at the centre reciting data from the patient notes to the pH Associates study monitor so that they can verify the data in the eCRF without the need to look directly at the identifiable source records. All people performing SDV will be trained by pH Associates.

All clinical data submitted will be checked for eligibility, completeness and accuracy and queries will be raised by the pH Associates data management team using agreed manual and programmed validation checks. Study centres will be required to co-operate with the data management team in the resolution of these queries.

Analysis of the primary endpoint will be independently reviewed by a member of the Data Analysis team at pH Associates who was not involved in the analysis of the final study data. No additional analysis checks will be carried out.

9.9. Limitations of the research methods

- Several sources of selection bias may be introduced in the study:
    - Patients treated as part of the CUP may differ from patients treated via private purchase and patients treated via NHS commissioning.
    - Patients were recruited from larger centres enrolled in the CUP, which may differ from smaller centres in terms of demographic and clinical characteristics, and therefore may not be representative of all real-world patients treated with InO.
- Patients may be lost to follow-up due to the occurrence of AEs, lack of efficacy or other reasons. The use of Kaplan-Meier curves to obtain estimates of median OS, RFS and time to CR/Cri takes into account patients' attrition.
- The interpretation of data collected retrospectively will be dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from the medical records. However, SDV will be employed to identify and correct abstraction errors.

- This is a descriptive study and no analyses to control for confounding will be carried out; therefore, no definitive causal relationships between InO and study endpoints can be made.

- The overall sample size of the study is relatively small, and therefore CR/CRi rates and MRD negativity rates may be estimated with relative imprecision, and 95% CIs may be relatively wide. In addition, the small sample size may not allow the conduct of univariate and multivariate Cox modelling to estimate the risk of VOD/SOS in patients with follow-up HSCT.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to ensure that only authorized study staff has access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

10.2. Patient Consent

The direct care team for each patient will be involved in extracting data and will produce pseudo-anonymized records from identifiable patient's records which will be collected for the purpose of this study, at all time preserving confidentiality. As this study involves pseudo- anonymized structured or unstructured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Patient Withdrawal

Not applicable

10.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

This study does not require IRB/IEC approval and an IRB/IEC review is not required as all confidential data will only be accessed via the direct care team. This protocol will be submitted for approval to the Health Research Authority.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE[13]), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP[13]), and EU General Data Protection Regulation (GDPR[14]), as appropriate.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The definition of an AE includes worsening of a pre-existing medical condition. A serious AE is any adverse drug reaction as defined above that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard.

A serious adverse drug reaction is a serious adverse event that is considered related to the medicinal product.

A hospitalisation meeting the regulatory definition for "serious" is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility. "Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

All AEs related to any *Pfizer product(s)* shall be reported to Pfizer Pharmacovigilance, Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Email Transmission**: GBR.AEReporting@pfizer.com; **Facsimile Transmission:** 0800 015 6401 (toll free);**Telephone Contact:** 0845 300 8031 (toll-free) or 0845 300 8032 (toll), *by the Principal Investigator at each centre or pH Associates* within 24 hours of discovery or notification. AE information must be recorded on the AE form emailed and/or faxed to **Email Transmission:** GBR.AEReporting@pfizer.com **Facsimile Transmission** Pfizer Pharmacovigilance; 0800 015 6401 (toll free) or 0845 300 8032 (toll) **Telephone Contact:** 0845 300.

Adverse drug reactions for non-Pfizer products should be notified by the Principal Investigator at each centre to the appropriate Marketing Authorisation Holder and/or to the Medicines and Healthcare Regulatory Authority (MHRA).

All pregnancies occurring in female patients while taking Pfizer products, and all pregnancies occurring in female partners of male patients taking Pfizer products should be reported to **Email Transmission:** GBR.AEReporting@pfizer.com; **Facsimile Transmission:** 0800 015 6401 (toll free), 0845 300 8032 (toll) **Telephone Contact:** 0845 300 8031 (toll-free) or 0845 300 8032 (toll). Pfizer Pharmacovigilance, Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS Email: GBR.AEReporting@Pfizer.com.

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be

based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the eCRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.*"*

All research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.
Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

11.1. Single Reference Safety Document

The InO Summary of Product Characteristics [15] will serve as the Single Reference Safety Document (SRSD) during the course of data collection part of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study will be reported according to the requirements of Strengthening the reporting of observational studies in epidemiology (STROBE)[16].

Authorship of publications arising from the study will follow the 2015 guidelines proposed by the International Committee of Medical Journal Editors (ICMJE)[17]. All authors will meet the criteria for authorship, and all people who meet the criteria will be authors. Potential conflicts of interest will be disclosed. All authors will have:

- made substantial contributions to conception or design or acquisition of data, or analysis and interpretation of data; AND
- participated in drafting the article or revising it critically for important intellectual content; AND
- approved the final version to be published.

Each author will meet all of these conditions and all individuals meeting these criteria will be authors. Acquisition of funding, collection of data, or general supervision of the research group does not justify authorship. Each author will have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new

information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	 B193 InO_Incl_Excl_criteria	15 08 2018	Inclusion and exclusion criteria for InO CUP
2	 INO1_Inotuzumab_rr_ Phpos and neg_Bcell_	06 09 2018	Inclusion and exclusion criteria for InO NHS Commissioning for adults

17. ANNEX 2. ADDITIONAL INFORMATION

Table 4. Dataset to be collected according to study time points

Variables	Study time points				
	Pre-index observation period	**Baseline**	**Index date**	**Post-initiation observation period**	**Other**
Date of birth (MM/YY)					✓
M/F					✓
ECOG performance status		✓			
InO first cycle: • dates of infusion • doses administered at each date, if dose is modified add reason for modification • date of end of cycle number • if decision taken to discontinue treatment: date discontinuation, reasons			✓	✓	
InO second cycle: • dates of infusion • doses administered at each date, if dose is modified add reason for modification • date of end of cycle number • if decision taken to discontinue treatment: date discontinuation, reasons					
InO additional cycles: • cycle number • dates of infusion • doses administered at each date, if dose is modified add reason for modification • date of end of cycle number • if decision taken to discontinue treatment: date discontinuation, reasons					
Response to InO treatment: • Treatment cycle number • Date response recorded • number of days into cycle response recorded					

Variables	Study time points				
	Pre-index observation period	**Baseline**	**Index date**	**Post-initiation observation period**	**Other**
• CR, CRi, no response, progression • MRD negative, MRD positive					
<u>If CR/CRi response to InO treatment is not recorded in patient's medical notes for a specific cycle,</u> then collect the following at time closest to the end of cycle to be able to infer CR/CRi and MRD negativity (see Annex 2 for operational definition): • Cycle number • platelets levels • ANC levels • peripheral leukaemic blasts • bone marrow blasts • Ongoing extramedullary disease in the visceral organs, lymph nodes, and the central nervous system: Yes/No (interval from date started to date resolved needs to include date of end of cycle)					
<u>If MRD negativity response to InO treatment is not recorded in patient's medical notes for a specific cycle,</u> then collect the following at time closest to the end of cycle to be able to infer CR/CRi and MRD negativity (see Annex 2 for operational definition): • Cycle number • PCR results providing percentage of leukaemic cells in bone marrow nucleated cells • Or alternatively, immunophenotyping by flow-cytometry results providing percentage of leukaemic cells in bone marrow nucleated cells					
ALL diagnosis: • Date of first diagnosis.	✓	✓			

Variables	Study time points				
	Pre-index observation period	**Baseline**	**Index date**	**Post-initiation observation period**	**Other**
• Phase of disease at receipt of Inotuzumab CR, 1st relapse, 2nd relapse , 3rd relapse, 4th or greater relapse • CD22-expression test results: positive/negative • Cytogenetic test result: MLL-AF4; BCR-ABL; low hypodiploidy/near triploidy; complex karyotype e • Relapsed at index date: Yes/No • Refractory at index date: Yes/No					
Liver diseases diagnosed prior to index date: • Name • date diagnosis • Diagnosed before/after ALL diagnosis • at index date, ongoing / resolved	✓	✓			
Full blood counts, date, result (including unit) for: • platelets • ANC		✓	✓		
Liver function tests: date, result and ULN for: • ALT • AST • ALP • Bilirubin • Albumin • gamma glutamyl transferase.		✓	✓	✓ for ALT, AST and bilirubin in patients with follow-up HSCT, at time of follow-up HSCT (up to 3 months before)	
Peripheral blood blast counts of patients				✓ in patients with	

Variables	Study time points				
	Pre-index observation period	**Baseline**	**Index date**	**Post-initiation observation period**	**Other**
				follow-up HSCT, at time of follow-up HSCT (up to 3 months before)	
ALL relapses prior to InO: • date of relapses • Name, start and stop dates, and best response to treatment for relapses prior to InO (list to be determined and may include: fludarabine- and anthracycline-containing regimens, blinatomumab)					
Treatment history for ALL (all since diagnosis) prior to InO: • 1st line chemotherapy according to national trial or treatment guideline • Blinatumomab treatment • Number of lines of salvage therapy • Prior HSCTs: number (0, 1, 2, ⩾3) and type of conditioning regimen for each HSCT: high-dose myeloablative, reduced-intensity, nonmyeloablative • CAR T-cell therapies: number (0, 1, ⩾2)	✓	✓			
ALL refractory prior to InO: • Name, start and stop dates, and best response to treatment prior to InO	✓	✓			
Concomitant medication to InO		✓ (if	✓	✓	

Variables	Study time points				
	Pre-index observation period	**Baseline**	**Index date**	**Post-initiation observation period**	**Other**
treatment: • Azole antifungal therapy including fluconazole, voriconazole, itraconazole and posaconazole: date started, date end		medication during InO treatment)			
AEs: name, date start, date end, grade, treatment given and response to treatment: • Documented diagnoses of VOD/SOS • grade 3/4 TRAEs affecting the lung, cardiac system, or kidney		✓		✓	
For each HSCT after initiation of InO: • date • InO treatment completed at HSCT: Yes / No • Conditioning regimens prior to HSCT including Busulfan other alkylating agents (names and date start, date end); full intensity / reduced intensity conditioning • Response to HSCT: CR, CRi, progressive disease, stable disease, alive/dead after HSCT				✓	
Chemotherapy treatment after initiation of InO: • name, regimen, start date • Response to chemotherapy treatment: CR, CRi, progressive disease, stable disease, alive/dead at end of treatment				✓	
CAR-T cell therapy after InO: • start date • response to CAR-T cell therapy: CR, CRi, progressive disease, stable disease, alive/dead at end of treatment				✓	
Patient status at the end of data collection period (alive/dead) • date of death / last clinic visit • Cause of death • If not known (i.e. lost to follow-up),				✓	

Variables	Study time points				
	Pre-index observation period	Baseline	Index date	Post-initiation observation period	Other
date of last recorded hospital visit.					

Note: All dates are DD/MM/YYYY for all patients, except for date of birth (MM/YY). If dates are not available as DD/MM/YYYY, dates will be recorded as MM/YYYY instead.

List 1. Operational definitions for clinical endpoints

Salvage therapy: therapy initiated in patients in whom initial induction therapy does not achieve remission (refractory ALL) or patients who entered remission and then subsequently relapsed (relapsed ALL), with the aim to induce remission of ALL.

Complete Remission (CR): defined as documented in medical records or (if unavailable in the records) as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, full recovery of peripheral blood counts (platelets $\geq 100 \times 10^9$/L and absolute neutrophil counts (ANC) $\geq 1 \times 10^9$/L) and resolution of any extramedullary disease.

Complete Remission with incomplete haematological recovery (CRi): defined as documented in medical records or (if unavailable in the records) as < 5% blasts in the bone marrow and the absence of peripheral blood leukaemic blasts, incomplete recovery of peripheral blood counts (platelets $<100 \times 10^9$/L and ANC $< 1 \times 10^9$/L) and resolution of any extramedullary disease.

Minimal Residual Disease (MRD) negativity: patients with ALL may be in remission (CR/CRi) although they may still harbour a large number of undetected malignant cells (MRD), and as such may be more susceptible to relapse. MRD describes diseases that can be diagnosed by methodology other than conventional morphology, and includes molecular methods like PCR, or immunophenotyping by flow-cytometry[18]. MRD negativity will be defined as documented in medical records or (if unavailable in the records) as leukaemic cells comprising $< 1 \times 10^{-4}$ (< 0.01%) of bone marrow nucleated cells.

CR/CRi Rate: proportion of patients who achieve CR/CRi at the end of treatment with InO.

MRD negativity Rate: the proportion of patients in whom MRD-negative status is observed at the end of treatment with InO (2-3 cycles of 3-4 weeks each in patients proceeding to follow-up HSCT, and up to 6 cycles of 3-4 weeks each otherwise).

Overall Survival (OS): time from index date to death. Patients will be censored at the end of the post-index observation period.

Relapse Free survival (RFS): time from index date to earliest date of the following events: death, progressive disease (including objective progression, relapse from CR/CRi, treatment discontinuation due to global deterioration of health status), and start of new induction therapy or post-therapy HSCT without achieving CR/CRi; as documented in medical records (if unavailable, infer using definitions above). Patients will be censored at the end of the post-index observation period.

Salvage therapy: Therapy initiated in patients in whom initial induction therapy does not achieve remission (refractory ALL) or patients who entered remission and then subsequently relapsed (relapsed ALL), with the aim to induce remission of ALL.